

Submission of Pre-Grant Opposition against Patent Application No. 6460/CHENP/2012

Dear Sir,

Date: 08-November-2017

This letter is in reference to submission of 'Pre-Grant Opposition' under section 25(1) of Indian Patent Act of 1970 concerning the patentability of the invention on the issue of 'Novelty' and 'Inventive Step' of the claims among other grounds against Patent Application No. 6460/CHENP/2012 dated July 23, 2012 titled: "Salts and polymorphs of 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6h-azepino[5,4,3-cd]indol-6-one" of whose the Applicant is PFIZER INC.

In view of the above, Pre-Grant Opposition along with the relevant form and documents is being enclosed for your kind consideration.

Thanking you.



Best Regards

Tapan Shah

BEFORE THE CONTROLLER OF PATENTS

CHENNAI

**REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT UNDER SECTION 25(1)
OF THE PATENTS ACT, 1970 AGAINST PATENT APPLICATION No. 6460/CHENP/2012
dated July 23, 2012**

Mr. Tapan Shah, E-13, UPSIDC-Site-IV, Kasna Road, Greater Noida - 201310 Uttar Pradesh, India

.....Opponent

-VS-

PFIZER INC., 235 East 42nd Street, New York-10017, United States of America.

.....Applicant

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Mr. Tapan Shah

**BEFORE THE CONTROLLER OF PATENTS
CHENNAI**

In the matter of Section 25(1) of The Patents Act,
1970 as amended by The Patents (Amendment)
Act 2005;

And

In the matter of The Patents (Second
Amendment) Rules 2006

And

IN THE MATTER of Indian Patent Application
No. 6460/CHENP/2012 dated 23/07/2012 in the
name of PFIZER INC., 235 East 42nd Street,
New York-10017, United States of America

.....Applicant

And

IN THE MATTER of representation by way of
opposition to the grant of patent thereto by
Mr. Tapan Shah, E-13, UPSIDC-Site-IV, Kasna
Road, Greater Noida - 201310 Uttar Pradesh,
India

.....Opponent

**STATEMENT OF CASE FOR REPRESENTATION UNDER SECTION 25(1) OF THE
PATENTS ACT 1970**

A. BACKGROUND OF THE OPPONENT

1. I, Mr. Tapan Shah, E-13, UPSIDC-Site-IV, Kasna Road, Greater Noida - 201310 Uttar Pradesh, India (hereinafter called “opponent”), make the following statement in support of the grounds of opposition submitted by me in opposing the grant of the patent application indicated in the cause title.

B. INDIAN PATENT APPLICATION NO. 6460/CHENP/2012

2. The Patent Application No. 6460/CHENP/2012 (hereinafter referred to as “the ‘6460 application”) titled “Salts and polymorphs of 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6h-azepino[5,4,3-cd]indol-6-one” entered national phase in India on July 23, 2012 from the PCT International Application No. PCT/IB2011/050571 dated February 10, 2011 which in turn claimed priority of February 12, 2010. The ‘6460 application was published on February 13, 2015.
3. The impugned ‘6460 application was filed in India with 25 claims broadly covering salts and polymorphic forms of 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one (i.e. Rucaparib) that are useful for the treatment of cancer, and pharmaceutical compositions containing the same. The complete specification of the ‘6460 application and the set of as-filed 25 claims as obtained from the IPAIRS (Indian Patent Application Information Retrieval System) database made available by the Indian Patent Office on its official website are attached herein as **Annexure I and Annexure II** respectively.
4. On September 13, 2012, the Applicant filed an amended set of 25 claims, attached herewith as **Annexure III**, which is being challenged by way of this pre-grant opposition.
5. A pre-grant opposition u/s-25(1) was filed by Cancer Patients Aid Association on Oct 10, 2017.
6. The impugned ‘6460 application is pending and awaits examination by the Indian Patent Office.

C. CLAIMS (LATEST/CURRENT) OF THE '6460 APPLICATION

7. The claims below represent the amended set of 25 claims filed by the Applicant on September 13, 2012.

Claims:

- 1. A camsylate salt of 8-fluoro-2-[4-[(methylamino)methyl]phenyl]-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one.*
- 2. The salt of claim 1, wherein the salt is crystalline.*
- 3. The salt of claim 1, wherein the salt is a crystalline anhydrous salt.*
- 4. The salt of any one of claims 1-3, wherein the camsylate is S-camsylate.*
- 5. The salt of any one of claims 1-3, wherein the camsylate is R-camsylate.*
- 6. The salt of any one of claims 1-5, wherein the salt has a powder X-ray diffraction pattern comprising one or more or two or more or three peaks at diffraction angles (2θ) selected from the group consisting of 12.2 ± 0.2 , 14.8 ± 0.2 and 22.4 ± 0.2 , wherein said powder X-ray diffraction pattern is obtained using copper K-alpha₁ X-rays at a wavelength of 1.5406 Angstroms.*
- 7. The salt of any one of claims 1-6, wherein the salt has a solid state NMR spectrum comprising one or more ¹³C chemical shifts selected from the group consisting of 213.4 ± 0.2 , 171.8 ± 0.2 , and 17.3 ± 0.2 ppm.*
- 8. The salt of any one of claims 1-7, wherein the salt has a solid state NMR spectrum comprising one or more ¹⁹F chemical shifts selected from the group consisting of -118.9 ± 0.2 and -119.7 ppm ± 0.2 .*
- 9. The salt of any one of claims 1-8, wherein the salt has a powder X-ray diffraction pattern comprising one or more or two or more or three peaks at diffraction angles (2θ) selected from the group consisting of 12.2 ± 0.2 , 14.8 ± 0.2 and 22.4 ± 0.2 obtained using copper K-alpha₁ X-rays at a wavelength of 1.5406 Angstroms; a solid state NMR spectrum comprising one or more or two or more or three ¹³C chemical shifts selected from the group consisting of 213.4 ± 0.2 , 171.8 ± 0.2 , and 17.3 ± 0.2 ppm; and a solid state NMR spectrum comprising one or more or two ¹⁹F chemical shifts selected from the group consisting of 118.9 ± 0.2 and -119.7 ppm ± 0.2 .*

10. The salt of any one of claims 1-9, wherein the salt is a substantially pure polymorph of S-camsylate polymorph Form A.
11. The salt of any one of claims 1-3, wherein the salt is a substantially pure polymorph of S-camsylate polymorph Form B or a substantially pure polymorph of S-camsylate polymorph Form C.
12. A maleate salt of 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one.
13. The salt of claim 12, wherein the salt is crystalline.
14. The salt of claim 12, wherein the salt is a crystalline anhydrous salt.
15. The salt of any one of claims 12-14, wherein the salt has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 6.0 ± 0.2 , 20.3 ± 0.2 , and 21.7 ± 0.2 , wherein said powder X-ray diffraction pattern is obtained using copper K-alpha₁ X-rays at a wavelength of 1.5406 Angstroms.
16. The salt of any one of claims 12-15, wherein the salt is a substantially pure polymorph of maleate polymorph Form A.
17. The salt of any one of claims 12-14, wherein the salt has a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of 7.5 ± 0.2 , 11.3 ± 0.2 , and 24.3 ± 0.2 , wherein said powder X-ray diffraction pattern is obtained using copper K-alpha₁ X-rays at a wavelength of 1.5406 Angstroms.
18. The salt of any one of claims 12-14 and 17, wherein the salt has a solid state NMR spectrum comprising one or more ^{13}C chemical shifts selected from the group consisting of 171.3 ± 0.2 , 112.4 ± 0.2 , and 43.8 ± 0.2 ppm.
19. The salt of any one of claims 12-14 and 17-18, wherein the salt has a solid state NMR spectrum comprising a ^{19}F chemical shift at $-123.1 \text{ ppm} \pm 0.2$.
20. The salt of any one of claims 12-14 and 17-19, wherein the salt has a powder X-ray diffraction pattern comprising: one or more or two or more or three peaks at diffraction angles (2θ) selected from the group consisting of 7.5 ± 0.2 , 11.3 ± 0.2 , and 24.3 ± 0.2 obtained using copper K-alpha₁ X-rays at a wavelength of 1.5406 Angstroms; a solid state NMR spectrum comprising one or more or two or more or three ^{13}C chemical shifts selected from the group

consisting of 171.3 ± 0.2 , 112.4 ± 0.2 , and 43.8 ± 0.2 ppm; and a solid state NMR spectrum comprising a ^{19}F chemical shift at -123.1 ± 0.2 ppm.

21. The salt of any one of claims 12-14 and 17-20, wherein the salt is a substantially pure polymorph of maleate polymorph Form B.

22. A pharmaceutical composition comprising the salt of any of claims 1-21.

23. A method of treating a mammalian disease condition mediated by poly(ADP-ribose) polymerase activity, the method comprising administering to a mammal in need thereof a therapeutically effective amount of the pharmaceutical composition of claim 22.

24. A method of treating cancer in a mammal, the method comprising administering to the mammal a therapeutically effective amount of the pharmaceutical composition of claim 22.

25. Use of a salt of any one of claims 1-21 in the manufacture for a medicament for the treatment of cancer.

D. GROUNDS OF OPPOSITION:

8. The opponent submits that the impugned '6460 application of the applicant is invalid and therefore the grant of the patent ought to be refused. The opponent relies upon the following grounds in the instant pre-grant opposition:
 - i. **Section 25(1)(b)(ii)** – that the invention so far as claimed in any claim of the complete specification of '6460 application has been published before the priority date of the claim in India or elsewhere, in any other document.
 - ii. **Section 25(1)(e)**– that the invention claimed in '6460 application is obvious and clearly does not involve any inventive step.
 - iii. **Section 25(1)(f)** – that the subject of any claim of the complete specification, is not an invention within the meaning of this act or is not patentable under this act.
 - iv. **Section 25(1)(h)** – That the applicant has failed to disclose to the Controller the information required by section 8 or has furnished the information which in any material particular was false to his knowledge.

9. **Prior Arts Referred to Herein:**

Document	Patent No. / Article	Publication Date/Year
D1	US 2006/0074073 A1	April 06, 2006
D2	WO 2008/114114 A2	September 25, 2008
D3	Delia A. Haynes et al. , “Occurrence of Pharmaceutically Acceptable Anions and Cations in the Cambridge Structural Database”, Journal of Pharmaceutical Sciences 2005, 94(10), Pages 2111-2120.	2005
D4	Bastin et al. , "Salt selection and optimisation procedures for pharmaceutical new chemical entities", Organic Process research & Development, Vol. 4, No. 5, Pages 427-435, 2000.	2000
D5	Stahl et al. , “Handbook of Pharmaceutical Salts Properties, Selection, and Use” Verlag Helvetica Chemic Acta, Switzerland, Zurich, 2002, Cover pages and pages 167-168, 170-173, and 216-217.	2002
D6	Stahl et al. , “Handbook of Pharmaceutical Salts- Properties, Selection, and Use” Verlag Helvetica Chemic Acta, Zurich, 2002, WILEY-VCH, pages 265-327.	2002
D7	Sherry L. Morissette et al. , “High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids”, Advanced Drug Delivery Reviews, 56 (2004), 275-300.	2004
D8	Stephen M. Berge et al. , “Pharmaceutical Salts”, Journal of Pharmaceutical Sciences, Jan 1977, 66(1), pages 1-19.	1977
D9	David P. Elder et al. , “The Utility of Sulfonate Salts in Drug Development”, Journal of Pharmaceutical Sciences 2010, 99(7), pages 2948-2961 (First published:	January 28, 2010

	January 28, 2010).	
D10	Rong Liu. , “Water-Insoluble Drug Formulation”, Interpharm Press, Denver, Colorado, 2000, Pages 525, 557-561.	2000

I. ENTITLEMENT TO PRIORITY:

10. The impugned ‘6460 application claims priority of US application no. US 61/304,277 dated February 12, 2010. The Opponent submits that a priority claim may be valid, only if there is an unambiguous disclosure in the priority application that enables direct derivation of the claim scope. In the present case, the claims of the impugned application recite R-camsylate salt of rucaparib and crystalline form C of the S-camsylate salt, which were neither cited expressis verbis in the priority document nor implicitly derivable therefrom.
11. Consequently, the subject matter of claims 1-3, 5-9, 11 and 22-25 of the impugned application is not entitled to claim the priority of US 61/304,277.

II. NOT AN INVENTION / NOT PATENTABLE U/S 3(d):

12. The invention claimed by the ‘6460 application is squarely covered by Section 3(d) in light of the submissions below, wherein the Opponent has clearly shown that 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one (i.e. Rucaparib) compound is disclosed in the existing prior art explicitly. What has been claimed by the Applicant is merely camsylate salt and maleate salt of rucaparib and polymorphic forms of such rucaparib salts, all of which are nothing more than mere new forms of a known substance. Additionally, the lack of any therapeutic efficacy of the alleged new forms over previously known form clearly renders the subject matter ineligible for the grant of a patent.

Section 3(d) bars "the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant."

Explanation – For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy."

13. NEW FORM OF A KNOWN SUBSTANCE:

14. The claims of the impugned '6460 application cover rucaparib compound in the form of a camsylate salt and a maleate salt. The claims of the impugned application also cover polymorphic forms of the camsylate salt and polymorphic forms of the maleate salt.
15. The prior art document D1, annexed herewith as **Annexure IV**, directly and unambiguously discloses 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one (i.e. rucaparib) free base as the "compound of formula 1" (D1, Abstract and Paragraph [0037]). In paragraph [0043], D1 also discloses camsylate and maleate salt forms of rucaparib. Similarly, the prior art document D2, annexed herewith as **Annexure V**, explicitly discloses rucaparib free base, a camsylate salt of rucaparib and a maleate salt of rucaparib (D2, page 1, lines 17-24; and page 7, lines 14-29, in particular lines 21 and 25). Thus by claiming a camsylate salt and a maleate salt of rucaparib and crystalline forms of such rucaparib salts, the Applicant has merely claimed new forms an already known compound.
16. In view of the above, the claimed rucaparib camsylate salt, rucaparib maleate salt or the polymorphic forms thereof can be considered as patentable u/s 3(d) only if an enhancement of known efficacy is demonstrated by the Applicant.

17. ENHANCEMENT OF KNOWN EFFICACY:

18. The Applicant in its '6460 application has mentioned that the problem solved by his invention is to provide further alternate salts of rucaparib and polymorphic forms thereof that are physically more stable and are not susceptible to hydration. The Applicant has further specified in his disclosure that the camsylate and maleate salts of rucaparib, and the polymorphic forms thereof possess advantageous properties in terms of bioavailability, stability, manufacturability and control of crystallization. The specification of the '6460 application, however, neither indicates any enhanced effect of the alleged rucaparib salts or their polymorphic forms, nor demonstrates any significance of such physicochemical properties with regard to 'therapeutic efficacy' in view of the known substance. To this end, one may take into consideration the law settled by Hon'ble

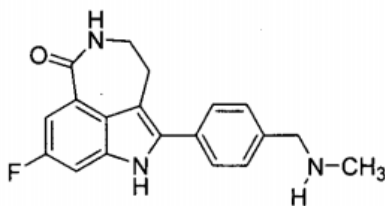
Supreme Court in the case-*Novartis vs. Union of India and Ors.*; *Natco Pharma Ltd. v. UoI & Ors.*; *M/S Cancer Patients Aid Association v. UoI & Ors.* decided on April 1, 2013. Refer excerpts:

*“The text added to section 3(d) by the 2005 amendment lays down the condition of “enhancement of the known efficacy”. Further, the explanation requires the derivative to “differ significantly in properties with regard to efficacy”. What is evident, therefore, is that not all advantageous or beneficial properties are relevant, but only such properties that directly relate to efficacy, which in case of medicine, as seen above, is its **therapeutic efficacy**.”*

19. It is therefore clear from the above submissions that the alleged camsylate salt and maleate salt of rucaparib and the polymorphic forms of such rucaparib salts are nothing more than mere new forms of a known substance. Additionally, the lack of any enhanced therapeutic efficacy of the alleged new salts and polymorphic forms thereof over previously known compound woefully fails to overcome the requirements of section 3(d) and clearly renders the subject matter ineligible for the grant of a patent. In the absence of any evidence for enhancement of known efficacy which has no basis in the specification of applicant's '6460 application, the claimed subject matter cannot be considered as patentable u/s 3(d).
20. The Applicant may make flagrant assertions of efficacy by illustrating alleged enhancements in physiochemical properties like physical stability, manufacturability, bioavailability, hygroscopicity, formulatability, etc. of the 'new' form; however, if the same does not translate to enhancement of known therapeutic efficacy, it fails the test of eligible subject matter under the proviso of Section 3(d) of the Act.
21. In view of the above submissions, it is therefore respectfully submitted that the subject matter as claimed in the impugned '6460 application is not patentable under section 3(d) of the Act.

III. LACK OF NOVELTY:

22. **Claims 1, 6-9, 12, 15, 17-20 and 22-25 of the impugned '6460 application lack novelty over the disclosure of D1.**
23. The prior art document D1 directly and unambiguously discloses 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one (i.e. rucaparib) free base as the “compound of formula 1” (D1, Abstract and Paragraph [0037]).



Compound of formula 1 of D1

24. More particularly, D1 discloses a dosage form containing rucaparib or a pharmaceutically acceptable salt thereof in an amount effective to inhibit the activity of poly(ADP-ribose) polymerase enzyme (D1, claim 5 and paragraph [0009]). In connection with pharmaceutically acceptable salts of rucaparib, D1 discloses a list of suitable pharmaceutical salts which explicitly includes rucaparib camsylate salt and rucaparib maleate salt (D1, Paragraph [0043]).

Paragraph [0043] of D1 describes that:

*“The phrase “**pharmaceutically acceptable salt(s)**”, as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in a compound. Compounds that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, **camsylate**, carbonate,.....iodide, isothionate, lactate, lactobionate, laurate, malate, **maleate**, mandelate,....., and valerate salts. Particularly preferred salts include phosphate and gluconate salts.”*

25. Further, the therapeutic uses disclosed in D1 clearly apply to all rucaparib salts disclosed therein, including the camsylate and maleate salts of rucaparib. Thus, the selection of camsylate salt and maleate salt from the disclosure of D1 does not result in novel subject-matter, since the selection is made from a single definite list of salts explicitly disclosed in paragraph [0043] of D1. Moreover, D1 describes procedures for the preparation of camsylate salt and maleate salt of rucaparib. D1 discloses that camsylate and maleate salts of rucaparib can be prepared by treating rucaparib free base with a substantially equivalent amount of the chosen organic acid in an aqueous solvent medium or in a suitable organic solvent, followed by evaporation of the solvent.

According to D1, camsylate and maleate salts of rucaparib can also be precipitated from a solution of rucaparib free base in an organic solvent by adding to the solution the chosen organic acid (D1, Paragraph [0051]). Thus, D1 provides a direct and unambiguous disclosure of camsylate salt and maleate salt of rucaparib.

26. The subject matter of claims 1 and 12 therefore lacks novelty in view of D1.
27. Claims 6-9, 15 and 17-20 of the impugned application define inherent properties of camsylate salt or maleate salt of rucaparib, i.e. a powder X-ray diffraction pattern of rucaparib camsylate or rucaparib maleate, solid state ¹³C-NMR chemical shifts, and solid state ¹⁹F-NMR chemical shifts. These inherent properties are also fulfilled by camsylate and maleate salts of rucaparib as disclosed in D1.
28. Thus, claims 6-9, 15 and 17-20 of the impugned application also lack novelty.
29. With respect to claims 22 to 25, D1 discloses and claims a dosage form for administration to a mammal, the dosage form comprising rucaparib or a pharmaceutically acceptable salt of rucaparib such as rucaparib camsylate or rucaparib maleate, in an amount effective to inhibit a poly(ADP-ribose) polymerase enzyme (D1, Claim 5 and Para [0043]). D1 further describes therapeutic methods of treating cancer in a mammal, which comprise administering to the mammal a therapeutically effective amount of a pharmaceutical composition containing a pharmaceutically acceptable salt of rucaparib such as rucaparib camsylate or rucaparib maleate (D1, Paragraphs [0043], [0062] and [0064]-[0065]).
30. In light of the above submissions, the opponent respectfully submits that the subject matter of claims 1, 6-9, 12, 15, 17-20 and 22-25 of the impugned '6460 application lacks novelty in view of D1 and as such is not patentable under section 2(1)(j) of the Patents Act.
31. **Claims 1, 12, 22 and 23 of the impugned '6460 application lack novelty over the disclosure of D2.**
32. D2 discloses 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one (i.e. rucaparib) as the "compound of formula 1" (D2, page 1, lines 17-23). D2 also discloses pharmaceutically acceptable salts of rucaparib which explicitly include rucaparib camsylate salt and rucaparib maleate salt (D2, page 7, lines 14-29, in particular lines 21 and 25). Thus, the camsylate and maleate salts of rucaparib are derivable directly and unambiguously from the disclosure of D2.
33. Regarding claims 22-23, D2 discloses pharmaceutical composition comprising rucaparib or a pharmaceutically acceptable salt of rucaparib such as rucaparib camsylate or rucaparib maleate,

and methods of using such composition for treating a mammalian disease mediated by poly(ADP-ribose) polymerase (D2, page 10, lines 12-16, 25-27; and page 11).

34. It is therefore respectfully submitted that the subject matter as claimed in claims 1, 12, 22 and 23 of the impugned '6460 application is not novel in any manner whatsoever.

IV. LACK OF INVENTIVE STEP:

35. Claims 1, 12, 6-9, 15, 17-20 and 22-25 of the impugned '6460 application lack Inventive Step over the disclosure of D1 alone:

36. It has already been demonstrated in the submissions made herein above that camsylate salt and maleate salt of rucaparib, and pharmaceutical compositions containing such rucaparib salts were already disclosed and described in the prior art document D1 and were publically known before the priority date of the impugned '6460 application. Further, the limitations as recited in claims 6-9, 15, 17-20 would be inherent in the disclosure provided by D1. Therefore, the subject matter of claims 1, 12, 6-9, 15, 17-20 and 22-25 of the impugned application, not being novel over the disclosure of D1, cannot be considered to involve an inventive step.

37. Furthermore, the subject matter of claim 25 of the impugned application does not qualify as patentable invention according to section 2(1)(j), and the subject matter of claims 23-24, being method of treatment claim, is clearly excluded from patentability as per Section 3(i) of the Patents Act as discussed herein below.

38. Claims 1, 12, 22 and 23 of the impugned '6460 application lack Inventive Step over the disclosure of D2 alone:

39. As shown above under the discussions of novelty grounds, the subject matter as claimed in claims 1, 12, 22 and 23 lacks novelty in view of the prior art document D2. Thus, the subject matter of claims 1, 12, 22 and 23 of the impugned application obviously cannot involve an inventive step.

40. Claims 1-25 of the impugned '6460 application lack Inventive Step over the disclosure of D1 in combination with the general knowledge in the art:

41. As outlined before, the camsylate salt and maleate salt of rucaparib lack novelty in view of D1. Merely auxiliary, the following arguments regarding lack of inventive step are additionally submitted.
42. D1 discloses 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one (i.e. rucaparib free base) as well as its pharmaceutically acceptable salts. In paragraph [0043], D1 explicitly teaches that camsylate and maleate salts are suitable pharmaceutically acceptable salts and are well suited for dosage form administration. Moreover, D1 describes procedures for the preparation of pharmaceutically acceptable salts of rucaparib. D1 teaches that pharmaceutically acceptable salts of rucaparib, including camsylate salt and maleate salt, can be readily prepared by treating rucaparib free base with a substantially equivalent amount of the chosen organic acid in an aqueous solvent medium or in a suitable organic solvent, followed by evaporation of the solvent. D1 further teaches that pharmaceutically acceptable salts of rucaparib can also be precipitated from a solution of rucaparib free base in an organic solvent by adding to the solution the chosen organic acid (D1, Paragraph [0051]). Therefore, a person skilled in the art would be motivated to make the camsylate and maleate salts of rucaparib because D1 points to these salts as pharmaceutically suitable salts, with the expectation of achieving similar results.
43. The camsylate and maleate salts of rucaparib are thus obvious and as such do not involve any inventive step.
44. In any event, a skilled person would know, as a matter of common general knowledge, that different salt forms may be used and screened for routinely in drug development. It would thus be obvious for a skilled person to conduct a routine screening procedure to identify a suitable salt for an active pharmaceutical compound in order to improve the compound's physicochemical properties such as physical stability, resistance to hydration, bioavailability, etc. Such routine procedure will lead the skilled person in an obvious manner to different salt forms of the active compound including the camsylate and maleate salts. In this connection, reference is made to documents D3-D6 which reflect the common general knowledge of the skilled person at the priority date of the impugned application.
45. D3, annexed herewith as **Annexure VI**, states that the use of salt formation as a means of varying the properties of pharmaceutical compounds is well known and well documented. D5 also states that salt formation can be used to improve stability and to reduce hygroscopicity of a drug product (D3, page 2111, left column).
46. D4, annexed herewith as **Annexure VII**, teaches that selection of an appropriate salt form for a new chemical entity provides the pharmaceutical chemist and formulation scientist with the

opportunity to modify the characteristics of the potential drug substance and to permit the development of dosage forms with good bioavailability, water solubility, stability and patient compliance (D4, Abstract). Moreover, D4 identifies maleate salt and camphorsulfonate/camsylate salt as common pharmaceutical salts (D4, page 428, right column, fourth paragraph; and page 433, left column, first paragraph below the table).

47. D5, annexed herewith as **Annexure VIII**, discloses that camphorsulfonic acid forms stable salts with many organic bases and so has found extensive use. Self-evidently, the compound of concern here, rucaparib, is an organic base compound (D5, page 217, item 8.3.4).
48. D6, annexed herewith as **Annexure IX**, identifies S-camphorsulfonic acid and maleic acid as suitable acids for making pharmaceutical salts (D6, pages 275 and 292).
49. According to the Applicant, camsylate and maleate salts of rucaparib are physically more stable and are not susceptible to hydration as compared to other salt forms of rucaparib, particularly phosphate salt of rucaparib, and are thereby more suitable for the preparation of solid dosage forms. Specifically, lines 5-20, page 17 of the impugned application are as follows:

[Page 17, lines 5-20] *“It has been found, as described herein, that Compound 1 can exist in multiple crystalline salt forms, such as maleate salt forms and camsylate salt forms.....Novel crystalline salt forms of Compound 1 have been discovered which are likely to be more suitable for bulk preparation and handling than other forms. For example, the phosphate salt of Compound 1, while particularly suitable, for example, for intravenous dosage forms, may be less suitable for a solid dosage form due to its susceptibility to hydration. Maleate and camsylate salt forms described herein (e.g., maleate polymorph Form B and S-camsylate polymorph Form A) exist as physically stable forms and are not susceptible to hydration as compared to other salt forms of Compound 1, making them particularly suitable in the preparation of solid dosage forms. In addition, maleate and camsylate salts described herein can be isolated in fewer steps than other salt forms in the synthetic process, allowing greater scope to control the crystallization.”*

50. The Opponent submits that the skilled person would have performed the salt screening with the expectation to obtain salts that are physically more stable and less hygroscopic than the phosphate salt of rucaparib. In this respect, for example, D7, annexed herewith as **Annexure X**, states that

the choice of counter-ion affects the properties of salt forms, including the degree of crystallinity, hygroscopicity, aqueous solubility, crystal habit as well as physical and chemical stability (D7, page 286, left column, lines 2-11). Moreover, D8, annexed herewith as **Annexure XI**, discloses that depending on the route of degradation, different salt forms impart different stability characteristics to the parent drug by various mechanisms. Differences in hygroscopicity of several salts influence stability of the drug in the dry state. In some cases, the salt-forming radical itself may enhance the stability of the parent drug (D8, Page 9, the paragraph bridging the left and right column). Since D1 provides moreover a description of the preparation of pharmaceutically acceptable salts of rucaparib, D1 represents the most promising starting point for solving the problems of the alleged invention of the impugned application.

51. Accordingly, the skilled person would have screened the salts described in paragraph [0043] of D1 for their physicochemical properties and would have selected the most stable and least hygroscopic salts for further development, i.e. in the present case, the camsylate and maleate salts of rucaparib.
52. As further evidence that the skilled person would have selected camsylate and maleate salts of rucaparib of D1, reference is made to D3 and D9. D3 investigated the occurrence of hydrates in the structures of salts of pharmaceutically acceptable counter-ions. Among the salts listed in table 2 of D3, the camsylate and maleate salts are mentioned as rarely forming hydrates and not showing extensive polymorphism (D3, page 2114, Table 2).
53. D9, annexed herewith as **Annexure XII**, confirms that sulfonate salts are usually less hygroscopic than other salts, that they are not prone to the formation of hydrates, and that they have much less propensity to form polymorphs (D9, the paragraph bridging pages 2951 and 2952, page 2952, left column, 3rd and 4th paragraph). According to D9, the camsylate salt is usually non-hygroscopic. (D9, Page 2954, table 4).

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Table 4. Summary of Physicochemical Properties of Salts of RPR200765 (Based on Bastin et al.²⁶)

Salt	Mp (°C)	Solubility (mg/mL)	pH (max)	Hygroscopicity
Hydrochloride	245–248	16.7	2.16	Hygroscopic, with multiple hydrated forms
Hydrobromide	276–277	3.3	2.63	Hygroscopic, with multiple hydrated forms
Mesylate	214	39.0	1.93	Nonhygroscopic with stable monohydrate form
<u>Camsylate</u>	265–267	20.0	2.22	<u>Nonhygroscopic</u>

54. Thus, the camsylate and maleate salts of rucaparib are rendered obvious by D1 as closest prior art, either alone or in combination with the general knowledge in the art.

55. Regarding claims 2 and 13, the opponent submits that mere provision of a crystalline form of a known pharmaceutically active compound cannot be regarded as involving inventive step. Further, it is well known in the art that crystalline forms are more stable and less hygroscopic than amorphous forms, and that crystalline compounds are generally easiest to isolate, purify, dry and, in a batch process, handle and formulate. In this regard, reference is made to documents D5 and D10 which reflect the common general knowledge of the skilled person at the priority date of the impugned application.
56. D10, annexed herewith as **Annexure XIII**, explains the hygroscopic nature of amorphous forms due to a lower density when compared to crystalline forms. Hence, it is readily apparent that amorphous forms typically do not show the same physical stability as crystalline forms, in particular they are generally more hygroscopic. This is further supported by D5, which on page 167, chapter 3.1., last paragraph, discloses that the counter-ion used for salt formation should yield a crystalline salt. D5 further explains that “lack of crystallinity (i.e. the salt was amorphous) normally would be expected to lead to severe problems and uncertainties, if the product intended to be developed is a solid, oral dosage form.” (emphasis added).
57. Therefore, a skilled person would have considered that a crystalline form of rucaparib salt as disclosed in D1 is a good starting point for drug development. That is, the skilled person would not have looked for amorphous forms, in particular when aiming at a salt form of rucaparib having improved physical stability and reduced hygroscopicity.
58. It is thus obvious to prepare a crystalline camsylate or a crystalline maleate salt of rucaparib of D1.
59. Claims 3 and 14 of the impugned application refer to camsylate or maleate salt of rucaparib in crystalline amorphous form. No unexpected or surprising effect seems to be associated with the anhydrous salt claimed in claims 3 and 14. The specification of the impugned application also does not throw any light on the importance or possible advantages associated with the anhydrous nature of the claimed salts that might be used in support of inventive step. Moreover, as evidenced by D5, it is generally established that an anhydrous form invariably shows higher solubility than hydrate forms (D5, Page 173, lines 1-2). As is demonstrated by the impugned application (see, Figures 8 and 14), the anhydrous form of the camsylate/maleate salt exists at low humidity and can be isolated upon drying. Accordingly, it is apparent that the anhydrous form would have obviously, or even automatically, been obtained by applying usual drying measures to the camsylate or maleate salt.
60. Claims 3 and 14 of the impugned application are thus not inventive.

61. The physical characteristics as recited in claims 6-9, 15 and 17-20 of the impugned application are inherent property of the camsylate salt and maleate salt of rucaparib. There can be nothing inventive, therefore, in measuring and reporting the physical characteristics of known camsylate and maleate salts of rucaparib.
62. Moreover, a skilled person would understand the regulatory interest in the polymorphic forms of a pharmaceutical compound and as such would be familiar with preparing a variety of polymorphic forms of pharmaceutical compounds as a matter of routine practice. The skilled person would be well aware that such preparations would include, at a minimum, crystallization from a variety of solvents at various temperatures. In addition, the skilled person would be familiar with routine methods of analyzing polymorphic forms of pharmaceutical compounds and that powder X-ray diffraction and solid state NMR are the most common methods for polymorphic characterization.
63. Thus, claims 6-9, 15 and 17-20 of the impugned application are rendered obvious by D1 as closest prior art, either alone or in combination with the general knowledge in the art.
64. Claim 10 of the impugned application recites the camsylate salt of rucaparib is a substantially pure polymorph of S-camsylate polymorph Form A. In claim 11, the camsylate salt of rucaparib is a substantially pure polymorph of S-camsylate polymorph Form B or Form C. In claim 16, the maleate salt of rucaparib is a substantially pure polymorph of maleate polymorph Form A, and in claim 21 the maleate salt is a substantially pure polymorph of maleate polymorph Form B. The designations "Form A", "Form B" and "Form C" are merely labels and do not limit the claimed salts in any way. Therefore, the subject matter of claims 10, 11, 16 and 21 should be disregarded when assessing the presence of inventive step.
65. Regarding claims 22 to 25, D1 discloses and claims a dosage form for administration to a mammal, the dosage form comprising rucaparib or a pharmaceutically acceptable salt of rucaparib such as rucaparib camsylate or rucaparib maleate, in an amount effective to inhibit the activity of poly(ADP-ribose) polymerase enzyme (D1, Claim 5 and Para [0043]). D1 further describes therapeutic methods of treating cancer in a mammal, which comprise administering to the mammal a therapeutically effective amount of a pharmaceutical composition containing a pharmaceutically acceptable salt of rucaparib such as rucaparib camsylate or rucaparib maleate (D1, Paragraphs [0043], [0062] and [0064]-[0065]). Claims 22-25 of the impugned application are thus not inventive.

66. For the reasons set forth above, it is therefore respectfully submitted that the subject matter of claims 1-25 of the impugned application is rendered obvious by D1 as closest prior art in combination with the general knowledge in the art and/or one or more of D3-D10.

V. NOT AN INVENTION/ NOT PATENTABLE UNDER SECTION 25(1)(f):

67. Section 25(1)(f) of the Patents Act, 1970 governs the case where the subject of any claim of the complete specification is not an invention within the meaning of this act, or is not patentable under this act.

68. NOT AN INVENTION / NOT PATENTABLE U/S 3(i):

69. The subject matter of claims 23-24 of the impugned '6460 application is squarely covered by Section 3(i) of the Patents Act, 1970 in light of the submissions below.

Section 3(i) of the Indian Patent Act bars, *"Any process for the medical, surgical, curative, prophylactic, diagnostic therapeutic or other treatment of human being or any process for a similar treatment of animals to render them free of disease or to increase their economic value or that of their products."*

70. The subject matter of claim 23 concerns a method of treating a disease condition mediated by poly(ADP- ribose) polymerase in a mammal in need thereof, using a pharmaceutical product. Similarly, the subject matter of claim 24 relates to a method of treating cancer in a mammal, the method comprising administering to the mammal a therapeutically effective amount of a pharmaceutical product. It is thus clear that claims 23-24 of the impugned application purport to claim a method for therapeutic treatment of human/animal subject, which is clearly excluded from patentability as per Section 3(i) of the Patents Act.

71. CLAIM 25 DOES NOT CONSTITUTE AN INVENTION UNDER SECTION 2(1)(j):

72. Claim 25 of the impugned application falls under section 25(1)(f) as it relates to use of a product in the manufacture of a medicament, and thus is not an invention within the meaning of this Act or not patentable under this Act.

The Patents Act 1970, in Section 2(1)(j) defines invention as follows: *"Invention" means a new product or process involving an inventive step and capable of industrial application.*

Section 2(1)(ja) defines inventive step as follows: *"Inventive step" means a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art.*

73. It is clear from the above definition that an invention to be patentable under the Indian Patent Act must be a new product or process involving inventive step and capable of industrial application. Not being product or process claim, the subject matter of claim 25 does not qualify as patentable invention according to section 2(1)(j) of the Act. It is further submitted that the 'use' of a pharmaceutical salt cannot be considered as a technical feature, whereas a claim should define a subject matter by technical features in order to fulfil the requirements with regard to inventive step.
74. Thus, the impugned application should be rejected on this ground alone.

VI. NON DISCLOSURE OF DATA REQUIRED UNDER SECTION 8:

75. It is humbly submitted that Applicant has attempted to evade the scrutiny of the Patent Office by not complying with the duty to disclose requirement under Section 8. Several decisions of the Hon'ble IPAB and various High Courts have clearly stated that the approach under Section 8 is a "strict liability" approach. In other words, there is no need to establish any adverse effect owing to non-disclosure of information that is required under Section 8. Simply put, mere non-disclosure is sufficient to challenge an application/ patent.
76. Under Section 8(1), according to several decisions of the Indian Courts and the IPAB, until the grant of the Indian patent, the Applicant is obligated to voluntarily bring to the notice of the Indian Patent Office detailed particulars with respect to its foreign applications on same/substantially the same invention or grant of such foreign patents. The reason for casting this obligation is to enable the Indian Patent Office to compare the scope of claims granted in foreign applications and the scope of claims sought in India.
77. The Applicant has made patent applications for the same subject matter in several countries including United States, European Union, China, Japan, Korea, Australia, etc., and these counterpart applications relate to the same subject matter as of the impugned '6460 application.
78. It appears from the file history of the impugned '6460 application that the Applicant filed latest Form-3 for the impugned application on 21st September 2015. After that, in spite of changes in the status of the corresponding applications in other countries, no further Form-3 updating the status was submitted in accordance with Section 8(1). Therefore, the Applicant failed to fulfill his

obligations and duty to disclose all information about the corresponding foreign patent applications to the Controller. The impugned '6460 application should thus be rejected on this ground alone.

79. It is respectfully submitted that upon detailed and careful analysis of the '6460 specification, several lacunae, infirmities, defects, insufficiencies and ambiguities are borne out. It is for this reason that the opponent has established various grounds of opposition under section 25(1) and the impugned '6460 application is therefore ought not to be granted.

E. RELIEF SOUGHT:

80. The Opponent states that it has established and made out a case on each of the aforesaid grounds of opposition and pray to the Learned Controller for the following relief(s):

- (a) Take on records the present representation
- (b) Leave to file further evidence
- (c) Opportunity to be heard
- (d) Refusal of the '6460 application in *toto*
- (e) Such other relief(s) as the Learned Controller may deem appropriate.

81. The opponent requests for a Personal Hearing before the Controller of Patents, before a decision adverse to the Opponent is taken in this matter.

Dated this 08th day of November 2017

Mr. Tapan Shah

To
The Controller of Patents,
Patent Office,
Chennai